Masterarbeit

MScPT 2017 ZHAW

Comparison of two commercially available devices to measure nitric oxide lung diffusing capacity in healthy, non-smoking adults, a randomized cross-over study.

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Datum: 17.05.2020

Anzahl Zeichen: 21853

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Abstract

Background: Lung diffusion measurements are commonly used for lung function diagnostics. The usage of nitric oxide (NO), in addition to carbon monoxide (CO) during a lung diffusion measurement, could lead to a better understanding of the process of diffusion. **Research Question:** This study investigated whether the two on the market available instruments for DLNO measurement ('MasterScreenTM' (MS) OFT Pro (Jaeger, Switzerland); 'HypAir' (HA) (Medisoft, Dinant, Belgium)), measure identical at the same time at the same place with the same protocol and with identical subjects. **Method**: This study followed a single-center randomized cross-over design carried out at the University Hospital of Zurich. 35 healthy subjects of mixed age and sexes were included and randomly allocated to perform slow spirometry, forced spirometry and lung diffusion measurements on either one of the devices. After completing all tasks, the participants performed the exact same maneuvers on the leftover device. The primary outcome was lung diffusion capacity for nitric oxide (DLNO). Secondary outcomes were lung diffusion capacity for carbon monoxide (DLCO), alveolar volume (VA) and breath hold time (BHT). Comparison of primary and secondary outcomes between both devices were calculated by using a linear mixed model. **Results:** The primary outcome DLNO showed a highly significant difference between the HA and the MS device. The mean difference was 24.1 mL/min/mmHg with a 95%CI of 21.8-26.4 mL/min/mmHg ($p<0.0001$). For DLCO the difference was not significant with a mean difference of -0.228 mL/min/mmHg (95%CI: -0.571 mL/min/mmHg and 0.116 mL/min/mmHg; $p>0.2$). The mean difference in alveolar volume between both devices was 0.484 L (95%CI: 0.447-0.512 L; $p<0.0001$). **Interpretation:** Although both devices show similar DLCO values, DLNO and VA showed systematic clinically relevant differences. There is no reasonable explanation to justify the difference.

Clinical Trial Registration: NCT04016597

Abbreviation List

BHT	Breath hold time
BMI	Body-mass-index
CO	Carbon monoxide
DLCO	Lung diffusion capacity with carbon monoxide
DLNO	Lung diffusion capacity with nitric oxide
HA	Device: HypAir
HE	Helium
ICC	Intra class correlation
MS	Device: MasterScreen
NO	Nitric oxide
SD	Standard deviation
SDws	Within-subject standard deviation
VA	Alveolar volume
95%CI	95 percent confidence interval

Introduction:

Lung-diffusion measurement analyzes the ability to absorb gases the air we breathe into the bloodstream.[1] This is one of the standard procedures in lung function diagnostics along with the body plethysmography and spirometry and is used in a wide variety of pulmonary disorders like chronic obstructive pulmonary disease (COPD), asthma and cystic fibrosis.[2–5] In current lung diffusion measurement carbon monoxide (CO) is added to the inhaled air to measure the difference of particles after exhalation within the exhaled air (DLCO).[6]

In contrast to DLCO, the lung diffusion capacity measurement with nitric oxide (DLNO) also uses the gas nitric oxide (NO) in addition to CO. This technique allows a more differentiated view on various reasons of a hindered gas diffusion.[7] It could help to better understand problems during the gas diffusion. This procedure in combination with the existing DLCO method could lead to a better understanding of lung diseases and could become of great value in diagnostic procedures.

By now only a small number of references-values for the DLNO method have been published and most of these include a limited number of subjects.[8–11] In the study of Zavorsky et al. (2017) the authors pooled data from previously held studies by Aulani et al. (2010), van der Lee et al. (2006) and Zavorsky et al. (2008) to create a bigger and therefore more representative pool of reference-values.[8,10–12] This was done although these reference-values were created with different protocols and obtained by different devices. In the study done by Munkholm et al. (2018) the researchers compared their obtained data with every single set of reference-values pooled by Zavorsky.[9] They illustrate that every single set of reference-values shows different means of the DLNO values. The authors state that possible explanations for these differences might be different protocols, different equipment as well as different populations.[9]

So far, a protocol has been published to standardize the DLNO measurement to eliminate future methodological bias[11]. Still different equipment is used internationally to measure the diffusing capacity and therefore leave room for potential bias. There are two commercially available devices on the market: ‘MasterScreenTM’ (MS) OFT Pro (Jaeger, Switzerland) and

'HypAir' (HA) (Medisoft, Dinant, Belgium). Both devices measure the NO concentration with an electrochemical cell.

A previously conducted pilot study, which aimed at a comparison of both devices reveals that the HA device constantly measures higher DLNO values (Radtke unpublished). Up to this point there has been no research published regarding a comparison of both devices, even though both are used within the field of research.

The aim of this study was to answer the question of whether the two on the market available instruments for DLNO measurement, measure identical at the same time at the same place with the same protocol and with identical subjects.

Method:

Design:

This study followed a single-center randomized cross-over design carried out at the University Hospital of Zurich. All included participants were invited to the research laboratory to perform spirometry as well as the diffusion capacity measurements. Subjects were informed about the project and asked for their consent to participate. After the randomization the participants performed the spirotemtries and the diffusion measurement on either one of the two devices. After completing all assessments on the first device the participants performed the exact same measurement on the second device. See section 'Protocol' for detailed information regarding the procedure.

Participants:

This study included 35 healthy non-smoking adults of both sexes and varying ages (>= 18 years). Recruitment was done by personal invitation or email. The Epidemiology, Biostatistics and Prevention Institute at the University of Zurich, the physiotherapy master's program at the Zurich University of applied Sciences (ZHAW) were places for recruitment. Inclusion criteria were >= 18 years, Caucasian ethnicity. Exclusion criteria were smoker, individuals with known pulmonary or cardiovascular disease, acute respiratory symptoms, operations or radiation therapy of the chest, a body mass index (BMI) >30kg/m^{-2} and pregnancy. The

subjects of the study live in Zurich or the surrounding area. Characteristics of the studied population are seen in Table 1.

Table 1

Patient characteristics at baseline

Variables	HA then MS	MS then HA	Complete
Subjects (n)	22 (63%)	13 (37%)	35
Sex			
male	11 (50%)	6 (46%)	17 (49%)
female	11 (50%)	7 (54%)	18 (51%)
Age (years)	40.8 ±2.9 (22-62)	38.8 ±5.2 (21-75)	40.0 ±15.5 (21-75)
Height (cm)	175.5 ±2.5 (159-200)	172.8 ±2.7 (159-196)	174.5 ±10.1 (159-200)
Weight (kg)	73.2 ±2.4 (53-91)	63.5 ±3.4 (47-91)	69,6 ±12.4 (47-91)
BMI ($kg*m^2$)	23.7 ±0.6 (18.6-28.1)	21.1 ±0.6 (17.1-23.7)	22,7 ±2.8 (17.1-28.1)
RHR	71.6 ±2.4 (50-95)	68.5 ±3.0 (51-88)	70.5 ±11.0 (50-95)
Spo2 (in %)	97.7 ±0.2 (95-99)	97.3 ±0.3 (94-99)	97.5 ±1.0 (94-99)

Data are mean inclusive standard deviation and range. BMI, body mass index; RHR, resting heart ratio; Spo2, oxygen saturation; MS, 'MasterScreenTM' OFT Pro (Jaeger, Switzerland); HA, 'HypAir' (Medisoft, Dinant, Belgium).

Randomization:

The allocation list was computer generated with the online randomization tool accessible at http/www.randomizer.org. Simple randomization has been used. The generated list contained numbers ranging from one to two. The number one implied the given subject started with the MS device and went on with the HA device. The number two indicated to start with the HA device and afterwards the MS device. The list was created by an independent person not involved in the study. Access to the list was restricted to two independent persons not involved in this study. Allocation concealment was ensured using central randomization, by

ad hoc request of the allocation sequence via phone. Blinding was not possible due to the protocol.

Ethics:

Since this study is of a methodological design focusing on a comparison of two devices and as it is not used for diagnostic purposes or treatment advice, it does not fall within the scope of the Human Research Act (HRA). Therefore, no authorization by the ethics committee was required. This has been examined and registered by the ethics committee of the canton of Zurich by means of a clarification of responsibilities (2019-02026).

Quality control:

The quality and reproducibility of the measurements were ensured by the following means. The devices were reviewed, and presets were made by technicians in advance of the study, to ensure that the devices were working properly. The software used for the HA device was 'Expair Version 1.32 05' for the MS device 'sentry Suite Version 3.0.2' was used. Each day the devices were manually calibrated using the three-flow method and a calibrated three liters syringe. Besides volume calibration, a gas calibration was performed using automated procedures for helium (He), carbon monoxide (CO), oxygen (O_2), and methane (CH^4). To ensure a detection of any major fluctuations in DLNO values during the course of the study, biological control measurements were performed. Therefore, the same subject performed every week all measurements on both devices, during the entire data collection period. This was done by two different subjects of both sexes (male, age: 26 years; female, age: 54 years).

Protocol:

In advance of the measurement, no intensive physical activities were allowed for at least 24 hours prior to testing. Coffee and meal consumption have been restricted three hours before undergoing the measurements. After welcoming the subject, the ad-hoc randomization has taken place by support of the statistical department. The aim of the study was explained to the subjects and the inclusion and exclusion criteria were checked. General information like bodyweight (nearest to 100g), standing height (nearest to 1 mm), sex, date of birth, resting heart rate (after a minimum of five minutes rest), oxygen saturation (in percent) as well as air

temperature (in degrees Celsius) and air-humidity (in percent) were noted. The measurements were taken at 430 meters above sea level. During the entire measurement, the subjects were asked to stay seated and could drink one cup of water in between the measurements. According to the randomization process, either one of the devices was used first. In the beginning, a slow spirometry was performed, and it was repeated until three reproducible measurements were collected. Afterwards, the forced spirometry was performed repeatedly until three reproducible measurements were gathered. Both spirometries were performed according to standardized protocols.[13] Following the forced spirometry, the lung diffusion capacity measurement was performed. Like the spirometry, standardized protocols were used for DLNO measurement and the maneuver was in the similar way repeatedly performed until three reproducible measurements (all DLNO scores within a range of 17 mL/min/mmHg), were collected.[14] In between the separate measurements a five-minute break as wash-out period was held. There were no changes to methods after trial commencement.

Outcomes:

The primary outcome of the measurements is DLNO (in mL/min/mmHg). Secondary outcomes are: DLCO (mL/min/mmHg), alveolar volume (VA; in liters) and breath-hold time (BHT; in seconds). Outcomes are obtained by stated DLNO devices. General information such as height, age and body weight were noted. Further values, for example BMI (body-mass-index) were calculated using patient characteristics.

Statistics:

Since there is no data available for of a power calculation, an a priori pilot study was used as a basis. From the values of the pilot study the ICC (Inter-Class-Correlation) for the DLNO values could be calculated as 0.96 (95% confidence interval (95%CI) 0.0.85-1). Because in the pilot study all participants were familiar with the procedure and that other external factors had an influence on the result, a more conservative approach was chosen for this study. For a desired ICC of 0.85 (95%CI 0.75-0.95) 31 participants were required (ICCest Calculation – Calculated with nQuery Advisor 7.0). Due to possible drop-out, 35 participants were recruited.

Comparison of primary and secondary outcomes between both devices will be calculated by using a linear mixed model (DLNO as primary endpoint) adjusting for device (Jaeger vs

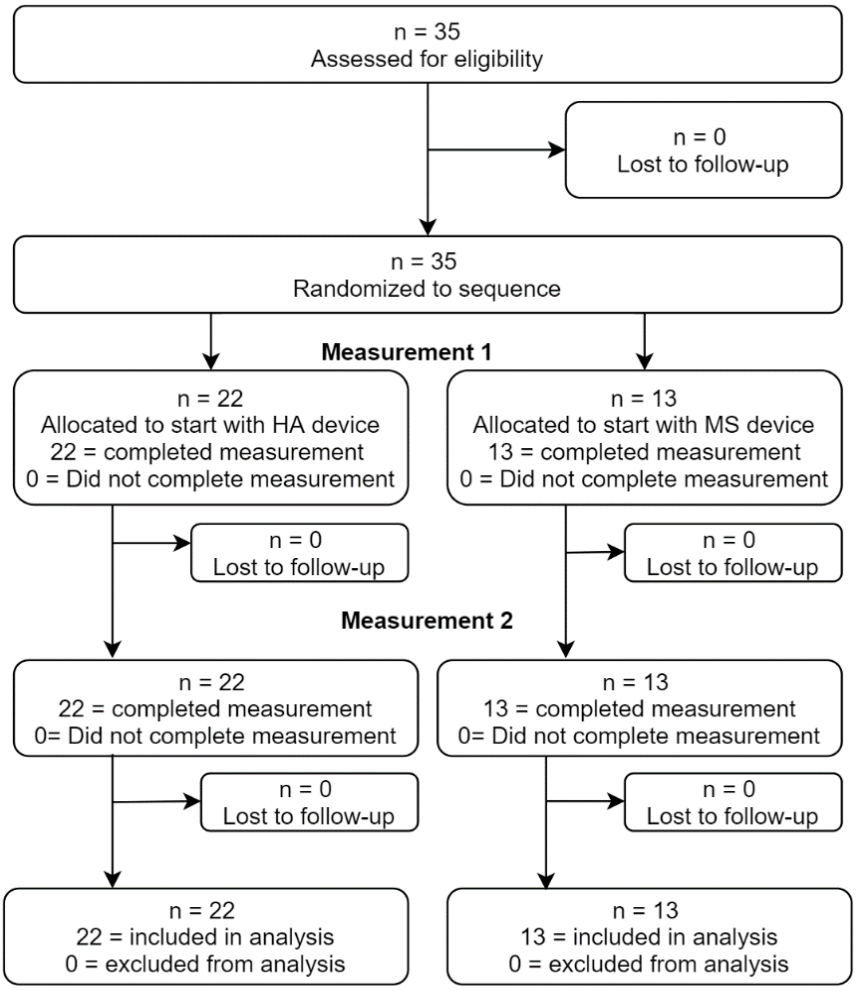
Medisoft, coded as 0, 1) and period (machine with which the participant started) as fixed effects AND random intercept for each subject.

The SPSS version 23 (IBM Corp. Armont, NY, USA) and R Version 3.6.3 (R-project, Vienna, Austria) are used for statistical evaluations. Three reproducible measurements per instrument (MS/HA) are at minimum required for calculation. The ICC 3.1 calculation (two way-mixed model) was used with its associated 95% confidence interval. Precision of DLNO values were be quantified by the within-subject standard deviations (SDws = root mean square error) calculated by the root-mean-square (RMS) method and the coefficient of variation.[15] Reproducibility was calculated with 1.96*1.96*√2*SDws (95% confidence interval). Intra-device reproducibility was calculated as 1.96 * √2 *SDws (95% level of confidence).[16] Intraclass correlation coefficients (ICC's) and their 95% CI's were calculated for the primary outcome using a two-way mixed model [consistency, single measurement, (ICC, 3.1)].[17] Interpretation of ICC's is based on Cicchetti.[18]

Results:

All participants completed all assessments and no participant was excluded from this study. No adverse events occurred during the entire data collection period. All participants were recruited and measured between October 2019 and January 2020. Trial was ended after completion of all measurements. No changes to outcomes after trial commencement were taken. See figure 1 detailed information about participant follow-up.

Figure 1
Flow diagram

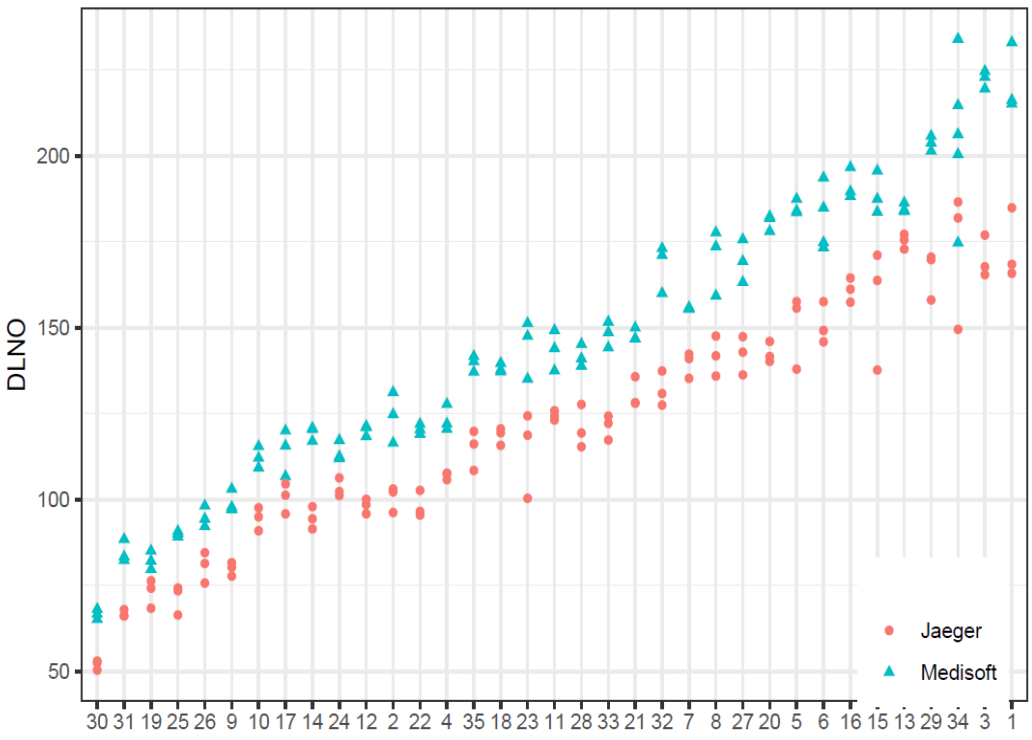


Flow diagram showing detailed information about patient follow-up. n, number of participants

Both sets of equipment passed all the tests performed. 22 Subjects were allocated to begin with the MA device, 13 allocated to begin with HA device. Subjects showed a mean resting heart rate of 70.5 (Standard deviation [SD]: 11.02; range: 50-95) and a peripheral capillary oxygen saturation of 97.7 (SD: 1.01; range: 94-99). Mean laboratory environmental conditions were: Temperature 23.7 °Celsius (SD: 1.66; range 21-27); Humidity 36.7 (SD: 8.96; range: 22.5-51). Allocation specific details are presented in Table 1.

The primary outcome DLNO difference between the HA and the MS device showed a highly significant difference. The mean difference was 24.1 mL/min/mmHg with a 95%CI of 21.8-26.4 mL/min/mmHg ($p<0.0001$). In figure 2 all DLNO results for each subject are plotted in ranked order.

Figure 2:
Ranked DLNO results



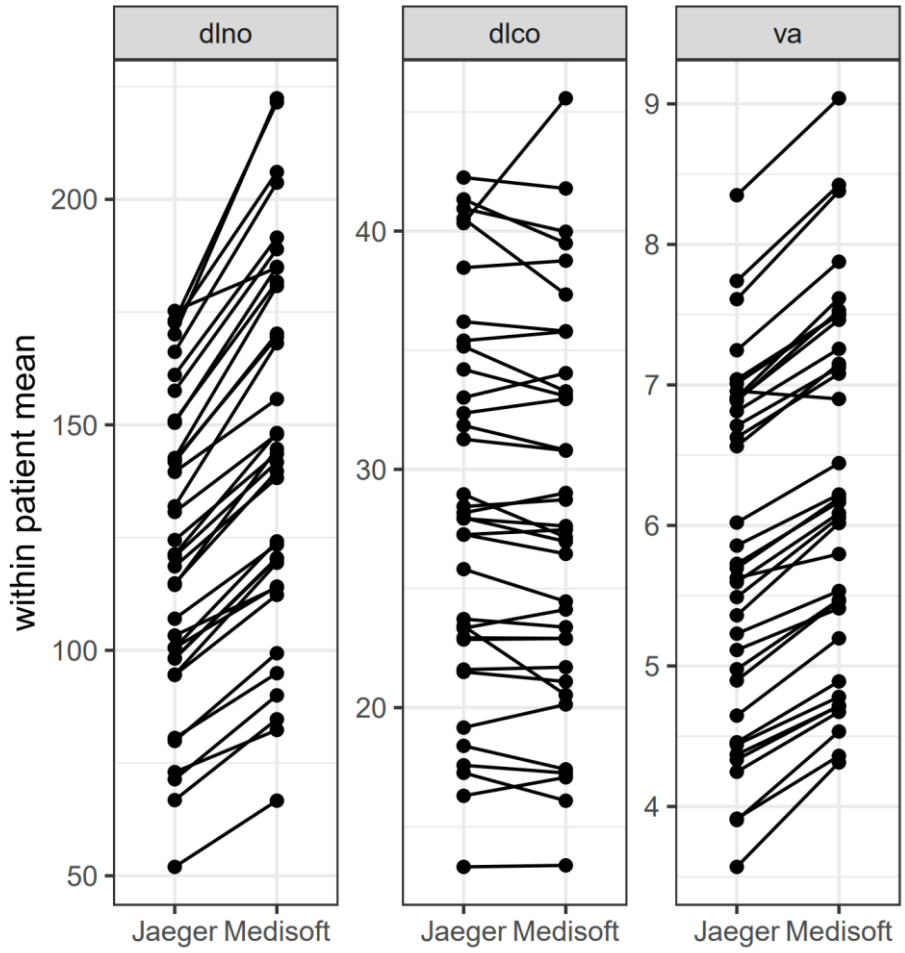
All DLNO measurements per subject id in ranked order for DLNO. DLNO, lung diffusion capacity measurement with nitric oxide; Jaeger, MasterScreenTM (MS) device; Medisoft, HypAir (HA) device.

In contrast to DLNO, the DLCO measurement show no significant difference with a mean difference of -0.228 mL/min/mmHg and a 95% confidence interval between -0.571 and 0.116 mL/min/mmHg ($p>0.2$). The mean difference in alveolar volume between both devices was

0.484 L (95%CI: 0.447-0.512 L; p<0.0001). The average Breath-hold-time on the HA device was 5.93 ±0.37, on the MS device the BHT was 6.29 ±0.34. Figure 3 shows mean values on both devices for DLNO, DLCO and VA. Mean values on both devices are linear connected.

Figure 3

Linear connected means



Linear connected means between both devices. DLNO, lung diffusion capacity measurement with nitric oxide; DLCO, lung diffusion capacity measurement with carbon monoxide; VA, alveolar volume; Jaeger, MasterScreenTM (MS) device; Medisoft, HypAir (HA) device.

Intra-device variability characteristics are shown in Table 2. All Subjects fulfilled the recommended intrasession repeatability criteria for DLNO and DLCO (17.0 and 3.2 mL/min/mmHg).[12,14] The reliability analysis showed an ICC for the DLNO value of 0.979 with a 95% confidence interval of 0.959-0.990.

Table 2

Intra-session variability

Variables	MasterScreenTM (MS)			HypAir (HA)		
	Measure-ment error [a]	Repeatability [b]	CV (%)	Measure-ment error [a]	Repeatability [b]	CV (%)
DLNO mL/min/mmHg	6.80	18.84	4.99	6.26	17,35	3,74
DLCO mL/min/mmHg	1.17	3.23	3.82	1.05	2.92	3.41
VA (L)	0.11	0.30	1.78	0.11	0.30	1.78

Data were measured at a target breath-hold time of 5 s. CV, coefficient of variation; DLNO, pulmonary diffusing capacity for nitric oxide; DLCO, pulmonary diffusing capacity for carbon monoxide; VA, alveolar volume.

[a] The measurement error (or within-subject standard deviation, SDws) was calculated by the root-mean-square (RMS) method.

[b] Repeatability of gas diffusing measurements was calculated as the SDws from three single-breath tests for each study visit separately and multiplied by 2.77 (95% level of confidence).

During the time of data collection for biomonitoring, both selected subjects completed each eleven biomonitoring assessments. Both subjects showed only little variation within their scores during the entire assessment period. Person one showed on the HA device a coefficient of variation of 3.17 mL/min/mmHg and a mean deviation of 6.13 mL/min/mmHg for DLNO. On the MS device a coefficient of variation of 3.07 mL/min/mmHg and a mean deviation of 4.56 mL/min/mmHg. Person two showed a coefficient of variation of 2.72 mL/min/mmHg and a mean deviation of 2.6 mL/min/mmHg for DLNO. On the MS device person two showed a coefficient of variation of 3.06 mL/min/mmHg and a mean deviation of 2.64 mL/min/mmHg.

Discussion:

The aim of this study was to compare two commercially available devices to measure DLNO.

This study shows that there is a statistically significant difference between both devices if comparing for DLNO. The within session repeatability for DLNO is about 17 mL/min/mmHg.[14,19] This study shows a higher mean difference (24.1 mL/min/mmHg; 95%CI: 20.5-27.6). It indicates that this difference is not only statistical but also clinically meaningful. In contrast to DLNO, DLCO show no statistically significant difference. The repeatability of DLCO is 2 -2.5 mL/min/mmHg.[20] Therefore, DLCO shows no clinical meaningful and no statistically significant difference between both devices. The coefficient of repeatability for VA for healthy subjects is 144 ml, consequently VA shows statistical significant and clinical meaningful differences.[21]

It is unclear how this systematic difference can be explained besides measurement differences. Both devices were running on the latest software update and have been controlled by technicians prior to this study, to ensure both are working properly. Both devices use similar electrochemical cells for the DLNO measurement. All instructions on both devices have been followed and the entire measurement procedure was held according to the latest protocol published by Zavorsky (2017).[12] A possible learning effect has been avoided by the cross-over study design. A possible carry over effect has been avoided by strict adherence to the wash-out period in between every single DLNO measurement and in between switching devices. Biomonitoring has been done during the entire data-collection period to detect any major fluctuations and have shown no major fluctuations whether in DLNO, DLCO or VA. Since there is no gold standard to compare these results with, these results cannot indicate whether one of both studied devices measures ‘correctly’. Therefore, no right or wrong can be stated by this study.

In a previous study by Zavorsky and Murias (2007) the intra-session variability of DLNO and DLCO was analyzed for 31 healthy subjects using the HA device.[19] Their observed intra-session variability values for DLNO are comparable to the ones obtained in this study (Repeatability: 19.5 versus 17.35 mL/min/mmHg). There is no data available for intra-session variability for

the MS device for healthy subjects. However, in our study, both devices show overall comparable intra-session variabilities.

The difference in calculated BHT can be explained by different software interfaces and slightly different instructions. Studies have shown that shorter breath hold times can overestimate the diffusion capacity in healthy subjects.[22,23] The HA devices scored lower BHT values and higher DLNO values. The study of Dressel et al. (2008) showed no statistically significant differences in DLNO if comparing a BHT of four to six seconds.[22] A comparison between four and eight seconds showed a statistically significant difference with an absolute mean difference of 8,63 mL/min/mmHg.[22] In this study the mean difference in BHT was 0.36 seconds and the mean difference in DLNO was 24.1 mL/min/mmHg. Therefore, the difference in BHT could only explain a marginal amount of the presented difference.

This study used different gas canisters with a different amount of helium percentage (10%HE for the MS device; 14%HE for the HA device). The usage of a mixture containing 14% Helium was recommended by the 'MediSoft' company during the purchase of the device. Although it is recommended to use 10% HE there are also studies published for DLNO reference values using a mixture with 14% HE.[10] Helium is used as tracer gas and has no interference with the measurement of DLNO. For the calculation of the alveolar volume a helium dilution technique was used on both devices. The dilution factor for HE was adjusted according to the mixture used for both devices.

Up to today only a small number of reference values for the DLNO method have been published, most of these include a limited number of subjects.[8–11] Most of these studies were performed in a single laboratory and used only a single device. To increase the amount of reference values, studies with larger samples sizes would be necessary. This would exceed the possibilities for a single laboratory. Therefore, multicentric studies must be performed to be able to test many subjects. Subsequently established data could be pooled to increase reference values. This study shows that it is not recommended to pool data collected by both devices (MS and HA) to create reference values as it is done before.[12] These would not represent true reference values for any given population.

In addition to these findings, it is at this point of time unclear if the same device presents similar values given the same circumstances for the same person at two different locations. This question must be answered in advance of pooling data from either one of the devices from different locations. These findings show that pooling data for reference values is currently not accurate. Further research and development must be conducted to allow pooling data from different locations.

One limitation of this study is the missing block randomization. This allowed the allocation to exceed a close to 50-50 percent distribution. In this study 63 % were appointed to start with the HA device. However, characteristics are well balanced along both sequence groups.

In conclusion, this study shows that the two on the market available devices for DLNO measurement ('MasterScreenTM' OFT Pro [Jaeger, Switzerland] and 'HypAir' [Medisoft, Dinant, Belgium]) present within the same individuals systematic statistical differences for the lung diffusion capacity measurement with nitric oxide. There was no clinical meaningful or statistical significant difference found for DLCO measurement at the same time. There is no reasonable explanation to justify the total amount of detected difference between both devices.

Acknowledgments:

This study was funded by the Epidemiology, Biostatistics and Prevention Institute at the University of Zurich in collaboration with the Zurich University of Applied Sciences (ZHAW). All equipment used in this study was bought independently. No third parties were involved in funding this study. The Author 'de Groot, Quintin' is the guarantor of the content of the manuscript, including the data and analysis. 'Radtke Thomas' designed the study and contributed to data analysis and interpretation. 'Sarah Haile' contributed to data analysis.

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Appendix:

1: Autorenrichtlinien des gewählten Journals:

CHEST®
Official Publication of the American College of Chest Physicians

AUTHOR INFORMATION PACK

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ISSN: 0012-3692

DESCRIPTION

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Journal Article

Sillen MJH, Speksnijder CM, Eterman R-MA, et al. Effects of neuromuscular electrical stimulation of muscles of ambulation in patients with chronic heart failure: a systematic review of the English-language literature. *Chest.* 2009;136(1):44-61.
Barker E, Haverson K, Stokes CR, Birchall M, Baily M. The larynx as an immunological organ: immunological architecture in the pig as a large animal model. *Clin Exp Immunol.* 2006;143(1):6-14.

In-Press Journal Article

Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA.* In press. https://doi.org/10.1001/jama.288.7.862

Book
Shields TW, LoCicero J III, Reed CE, Feins RH. *General Thoracic Surgery.* 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009:200-232.

Book Chapter
Stone AC, Klinger JR. The right ventricle in pulmonary hypertension. In: Hill NS, Farber HW, eds. *Pulmonary Hypertension*. New York, NY: Humana Press; 2008:93-126.

Abstract
Garg N, Garg G, Christensen G, Singh A. Acute coronary syndrome caused by coronary artery mycotic aneurysm due to methicillin-resistant *Staphylococcus aureus* [abstract]. Chest. 2008;134(suppl):1001S.

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References: American Medical Association. *AMA Manual of Style: A Guide for Authors and Editors.* 10th ed. New York, NY: Oxford University Press; 2007.

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Inclusive language acknowledges diversity, conveys respect to all people, is sensitive to differences, and promotes equal opportunities. Articles should make no assumptions about the beliefs or commitments of any reader, should contain nothing which might imply that one individual is superior to another on the grounds of race, sex, culture or any other characteristic, and should use inclusive language throughout. Authors should ensure that writing is free from bias, for instance by using 'he or she', 'his/her' instead of 'he' or 'his', and by making use of job titles that are gender neutral (eg, "chairperson" instead of "chairman" and "flight attendant" instead of "stewardess").Guidance

GUIDANCE FOR SPECIFIC ARTICLE TYPES
In addition to following the general manuscript preparation instructions, authors should refer to the specific instructions for the type of article they are submitting.

1 **Section Consider Unsolicited (Y/N[a]) Abstract (wd max) Text[b] (wd max) References (max)**
Original Research Y 300 3,200 50 **Guidelines and Consensus Statements** Y 300 4,000 150
Invited Content[a] CHEST Reviews N 250 3,500 75 How I Do It N 250 3,000 50 Point/Counterpoint Editorials N None 1,200 12 Editorials N None 1,000 12 Special Features N 250 3,500 75 **Case Series** Novel Reports Y 150 750 20 Chest Imaging & Pathology for Clinicians Y None 1,600 10 CHEST Pearls Y None 1,600 10 Ultrasound Corner Y None 1,600 10 Correspondence Letter to the Editor Y None 400 5 Response to Letter to the Editor N None 400 5 Research Letter Y None 1,000 10 General Interest Commentary and Announcement Y None 1,000 5

[a]These article types are invited. Authors with ideas for topics are encouraged to contact *CHEST* with proposals at editorialoffice@chestnet.org. [b]Text word counts exclude abstract, references, figure legends, and tables.Original Research

Original Research
1 **Article Element Requirements** Abstract length 300 words, structured format, include clinical trial information for randomized controlled trials Text length 3,200 words Reference count 75 references

Format
A structured abstract should be provided. The abstract should be divided into the following sections: Background, Research Question, Study Design and Methods, Results, Interpretation, and Clinical Trial Registration Number (where applicable). The body of the text should be divided into the following sections: Introduction (not labeled), Methods, Results, Discussion, and Interpretation. Acknowledgements can follow (including author guarantor statement and contributions), then References. Finally, a Take Home Point pullout will be published. Please provide a sentence for the Study Question, Results, and Interpretation.

Institutional Review Board (IRB) Approval
Most Original Research manuscripts must include a statement relating to institutional review board (or equivalent) approval in the "Methods" section. *CHEST* requires that authors include the committee name and approval number. In multicenter studies, the list of relevant committees and approval numbers may be included as an e-Appendix. See more information on IRB approval here.

Randomized Controlled Trials (RCTs)
CHEST defines a randomized controlled trial (RCT) as"any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes." Authors preparing reports of RCTs for submission to *CHEST* should follow the CONSORT (Consolidated Standards of Reporting Trials) checklist and must include a CONSORT flowchart as Figure 1. Templates for the generation of CONSORT flowcharts are available online.

In addition to following CONSORT, *CHEST* requires investigators to register their clinical trials in an approved public trials registry(see Registration of Clinical Trials and Systematic Reviews below). Purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator) do not require registration.

Systematic Reviews and Meta-analyses

Authors preparing systematic reviews and meta-analyses for submission to *CHEST* should follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) checklist and must include a PRISMA flow diagram as Figure 1 on submission. CHEST strongly encourages registration of systematic reviews with the PROSPERO registry (see Registration of Clinical Trials and Systematic Reviews below). Additionally, authors are expected to address all items in the checklist in the writing of the manuscript. Those seeking additional guidance regarding the preparation of a systematic review can also consult the Cochrane Handbook for Systematic Reviews of Interventions at http://www.cochrane.org/handbook and the Institute of Medicine's Standards for Systematic Reviews available at http://www.nationalacademies.org/hmd/Reports/2011/Finding-What-Works-in-Health-Care-Standards-for-Sy of Trials

Registration of Clinical Trials and Systematic Reviews

Authors of reports of clinical trials and systematic reviews should record their investigations in a viable registry (eg, ClinicalTrials.gov, PROSPERO [https://www.crd.york.ac.uk/prospero/]). Approved public trials registries are those that meet the criteria established by the World Health Organization (WHO). To register a trial, authors must submit the details directly to any one of the WHO primary registries. CHEST reserves the right to reject papers if it deems the disclosure at the registry to be incomplete. An IRB statement is not a substitute for an approved clinical trial registration.

Authors should update their registrations to reflect any changes in outcomes, including primary and secondary end points, or protocols before participants are enrolled. The methods described in the published report must accord with those previously published in the study registration to avoid even the appearance of scientific misconduct. Furthermore, any changes to the original registration (eg, substituting a secondary outcome as the primary outcome) should be described in detail in the Methods section of the manuscript. Authors who modify their methods should post those changes on the online registry before submitting their manuscripts to *CHEST*.Studies

Surveys/Questionnaire-Based Studies

Investigators who administer surveys and questionnaires as part of their study should obtain copyright permission if needed; no surveys should be adapted without the permission of the developer. Any unapproved changes in how PRO instruments are used or approved changes that have not been psychometrically studied and found to be reliable and valid will invalidate the results.

Authors of studies based on surveys or questionnaires should report on data that have been collected within two years of submission, including supporting reliability and validity data. All survey-based studies should describe the method used to achieve the response rate (eg, Dillman's tailored design method) and should provide a convincing rationale for why lower response rates provide important and generalizable information. Nonrespondents should be characterized well enough to allow for assessment of potential for nonresponse. Authors are encouraged to report outcome rates for most surveys using standardized definitions and metrics (eg, those proposed by the American Association for Public Opinion Research). This information must be detailed in the methods section.

Other Study Types

The Equator Network provides checklists for other types of studies such as the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement. Checklists are also available for cohort, case-control, and cross-sectional studies, and authors are encouraged to follow these.

Confidence Interval

For clinical studies, the primary outcome should be expressed as the difference between groups with a confidence interval (CI) around that difference provided in the Abstract and in the main article. In most cases, P values should not be presented without an accompanying effect estimate and CI. The CI is useful to readers because it indicates the precision of an estimated population value.

Matching Language to Level of Evidence Guidelines

CHEST endorses the HEART Group Statement[1] calling for better matching language in original research to the evidence found in different study designs.[2] In short, in observational studies investigators should use descriptive statements such as "we observed a lower risk" rather than a more definitive statement such as "reduced the risk by" that are more appropriate to RCTs.Editors of Heart Group Journals. Statement on matching language to the type of evidence used in describing outcomes data.J Am Coll Cardiol. 2012;60(23):2420. Kohli P, Cannon CP. The importance of matching language to type of evidence: avoiding the pitfalls of reporting outcomes data. Clin Cardiol. 2012:35:714-717. Guidelines

Guidelines and Consensus Statements

1 **Article Element Requirements** Executive summary Provided in bold text and including one to two paragraphs of introduction, followed by a summary of the data and a bulleted list of all recommendations and suggestions included in the document Abstract length 300 words, structured format Text length 4,000 words (may be negotiated with *CHEST*)

CHEST Guidelines are generated by CHEST under a well-defined development process. Committees work closely with the Guideline Oversight Committee, the Editor in Chief of *CHEST*, and relevant Associate Editors in developing guideline articles intended for submission to *CHEST*.

CHEST will work with other guideline-producing organizations where the possibility of mutual benefit exists. This includes guidelines and consensus statements where CHEST (the organization) has either agreed to participate in the development process, or has agreed to endorse the guideline or statement, or has been uninvolved in the development process.

Guideline-producing organizations that are not connected to a journal may submit their guideline for publication in *CHEST*. The submission will undergo peer review to include review by an internal methodologist and member of the CHEST Guideline Oversight Committee. For guidelines produced by organizations that publish in a subspecialty journal, a summary of the guideline publication with implementation tools may be published in *CHEST* with the goal of reaching our broad clinical audience. For these types of projects, authors should Contact the Editor in Chief of *CHEST* prior to submission. Recognize that a formal review of the submission will take place before a publication decision is made. Consider including implementation tools in the document or as a supplement. The Institute of Medicine's Standards for Developing Trustworthy Clinical Practice Guidelines should be consulted for guidance when using systematic reviews as the basis for guideline recommendations; these are available at http://www.nationalacademies.org/hmd/Reports/2011/Clinical-Practice-Guidelines-We-Can-Trust.aspx. Invited Content

Invited Content

Reviews

CHEST Reviews

1 **Article Element Requirements** Abstract length 250 (narrative) Text length 3,500 words Reference count 75 max

CHEST reviews in "sub-specialty" (eg, "Asthma", or "COPD") can include clinical, translational, ethics, education, and practice management topics. When a topic does not neatly fit in a sub-specialty section it may be included in the Special Features section (see below).

CHEST reviews are state-of-the art concise reviews on focused clinical, translational, ethics, education, and practice management topics. These should include a description of the importance of the topic and a summary of what is known about the topic with special attention to the most recent advances impacting practice. When relevant, authors should consider including sections on anticipated future advances, the authors' perspective on the topic, and summary tools that could assist with the application of the review in practice (eg, summary tables, algorithms). Topics in this section are developed and invited by the *CHEST* Associate Editors and Editor in Chief. Authors with suggestions for a topic are encouraged to contact CHEST at editorialoffice@chestnet.org.How I Do

How I Do It

1 **Article Element Requirements** Abstract length 250 words (unstructured) Text length 3,000 words Reference count 50 max

The How I Do It Section includes practical reviews of well-defined clinical questions with tools to assist with addressing the question when faced in practice. A relevant clinical question may have good evidence and guidelines available to support the approach, but implementation assistance is needed, or have weak evidence to support an approach but is a question with which clinicians struggle in practice.

Articles should be organized as follows: A well-defined clinical or procedure-related question. Case example. Review of relevant literature. Comment on nuances when applying to patient care. Review of relevant guidelines. Comment on nuances when applying to patient care. A summary table or algorithm whenever relevant. Summary of the approach to the question. Suggestions for multimedia adjuncts to the article are welcome.
Manuscript for the How I Do It section are invited by the subspecialty editorial teams.
Unsolicited contributions will not commonly be considered. Authors with ideas for topics should contact *CHEST* at editorialoffice@chestnet.org before preparing a manuscript.Point

Point/Counterpoint Editorials

Point/Counterpoint editorials are submitted in two stages, each with distinct requirements: the Point and Counterpoint pieces have longer word limits, and the rebuttals are intended to be more succinct.

Point/Counterpoint:

1 **Article Element Requirements** Abstract length None Text length 1,200 words Reference count 12 references Figure/table limits 3 total tables and figures (not 3 of each)

Rebuttals:

1 **Article Element Requirements** Abstract length None Text length 500 words Reference count 7 references Figure/table limits 1 figure or table

Point/Counterpoint Editorials present a debate by content experts with different interpretations of the evidence supporting an approach to a topic. Authors on each side of the debate develop a rationale for their stance and then are given an opportunity to view and respond to the rationale provided counter to their stance.

Point/Counterpoint Editorials are invited by the editorial team. Authors with suggestions for a topic should contact *CHEST* at editorialoffice@chestnet.org prior to developing a manuscript.Editorials

Editorials

1 **Article Element Requirements** Abstract length None Text length 1,000 words Reference count 12 max

Editorials are invited by the editorial team. They are meant to allow a content expert to discuss the findings of an original research article, sharing their perspective on how the publication advances the field, impacts practice, and highlights further research needs.Special Features

Special Features

1 **Article Element Requirements** Abstract length 250 words, narrative format Text length 3,500 words Reference count 75 references

Special Features are invited reviews, commentaries, and other items of interest that do not fit well into other categories. NOTE: Systematic reviews should be submitted as Original Research. *CHEST* will consider unsolicited Special Feature submissions, but authors must be aware that at any given time *CHEST* also has a long list of pending invited topics. Authors are encouraged to contact *CHEST* at editorialoffice@chestnet.org with a proposal on the topic prior to the writing or submission of any Special Feature articles.Case Series

Case Series

Novel Reports

Novel Reports (Online only)

1 **Article Element Requirements** Abstract length 150 words, narrative format Text length 750 words, for a single case report; 1,600 words for multiple cases Reference count 20 references Format Introduction, Case Report(s), Discussion Other Written patient permission is required for publication

Case report submissions to *CHEST* should describe a new entity, mechanism, presentation, means of diagnosis, or treatment of a disease. All submissions to this section must be novel and/or unique. It is appropriate to submit a single case or multiple cases highlighting the same message. Studies with a research question that is addressed by a case series should be submitted as original research.

Case reports do not need institutional review board approval, but authors must preserve patient privacy and follow the Health Insurance Portability and Accountability Act or national equivalent rules in writing up the case. On acceptance, *CHEST* will require submission of written patient permission for publication. It is acceptable to submit case reports to *CHEST* that have been presented at meetings and congresses. This information should be disclosed on the title page and provided in the references.Chest Imaging

Chest Imaging and Pathology for Clinicians (Online Only)

1 **Article Element Requirements** Abstract length None Text length 1,600 words (of which clinical, radiologic, and pathologic findings and discussion should be approximately 500 words each) Reference count 10 references Format Case Presentation (with distinct Clinical, Radiologic, and Pathologic Findings subsections); Q: What is the Diagnosis; A: Diagnosis; Discussion (with distinct Clinical, Radiologic, and Pathologic Discussion subsections); Bulleted list (3-4 lines at the most) of the take-home message from the case. Other Written patient permission is required for publication

Chest Imaging and Pathology for Clinicians is designed to aid readers in understanding the connection between clinical, radiographic, and pathologic features of a disease state. Each submission should include distinct clinical, radiologic, and pathologic sections within the case presentation and the discussion.

The format for submission to this section is as follows: **Title**: should include a short summary of the presenting feature, but not the diagnosis (ie, Dyspnea with slow-growing mass of the left hemithorax) **Case Presentation**: should include the following sections in sequence without the use of subheadings and without giving away the diagnosis: A clinical findings section should mention the relevant positives and negatives while avoiding detailed description of hospital course. The focus should be on the approach taken by the authors to make the diagnosis. Comments on the differential diagnosis and a table summarizing the clinical and radiologic features of the differential diagnoses are desirable. A radiologic findings section should briefly detail the plain chest radiograph (no corresponding figure need be submitted) and describe in detail the additional imaging studies performed, emphasizing findings that point to the diagnosis A pathologic findings section should describe these findings in detail and should focus on correlations with the radiologic findings. The pathology presented should confirm the diagnosis. Gross pathology or high-quality, low-power images that capture the radiologic and pathologic correlation are recommended. **What is the diagnosis?** Alternative questions may also be included (ie, What study should be conducted next?) in addition to the diagnosis question. **Diagnosis: XXX**; should also include the answer to any other questions posed **Discussion** should include the following sections in sequence with the use of subheadings **Clinical discussion** should illuminate how the clinical findings tie in with the diagnosis, addressing the typical and atypical case features. Authors are encouraged to highlight the clinical features that may alert the clinician to the diagnosis. In case of a rare disease, and brief description as well as diagnostic tests/criteria should be included. These may be tabulated. In the last paragraph, the outcomes of the case and the result of described intervention are useful. **Radiologic discussion** should highlight specific findings from chest radiographs and CT, PET, and MR scans. Authors are encouraged to highlight findings that exclude diagnosis and elaborate on the use of particular modalities. **Pathologic discussion,** should highlight pathologic patterns of lung involvement that correspond to patterns seen on chest imaging, and the pathologic differential diagnosis of the disease under discussion should be presented. Special staining techniques that may allow the diagnosis to be established should be addressed. **Conclusion**: a bulleted list (3-4 lines at the most) of the take home message from the case for clinicians is encouraged. **Image Quality Considerations**

Sizing: Images should be appropriately sized to minimize superfluous information—including, in particular, any surrounding structures outside the body. Labeling/Figure legends: Legends should include baseline information: slice thickness (in mm), orientation (axial, coronal), and reconstruction

algorithm (in the case of lung, either "smooth" or "edge enhanced" or their equivalent). For contrast-enhanced pulmonary artery studies, provide the rate, timing, volume and type of contrast as appropriate. Additional Imaging techniques: of particular interest is the addition of "movie" files (AVI or equivalent) when these augment image interpretation (eg, cardiac, aortic, or general vascular cases). The inclusion of other standard imaging formats, such as volumetrically rendered images and maximum (MIPS) and minimum (MinIPS) projection images, can be helpful. CHEST Pearls

CHEST Pearls

1 **Article Element** Requirements Abstract length None Text length 1,600 words (of which case presentation should be under 300) Reference count Up to 10 references listed under a heading of "Suggested Readings." in chronological order; no citations in text. Format See below Other Written patient permission is required for publication

Manuscripts for this section are designed to present a case, pose a question, provide the answer, and summarize the main teaching points as Pearls.

Title should include a short summary of the presenting feature, but not the diagnosis. **History** should provide the recent clinical presentation with relevant past medical history, with enough information regarding relevant positives and negatives to allow construction of a reasonable differential diagnosis. **Physical Examination Findings** should give the patient's vital signs and other physical findings labeled according to organ system (eg, chest: bibasilar rales; cardiac: grade II/VI holosystolic murmur at the apex radiating to the axilla; abdomen: non-tender without organomegaly). **Diagnostic Studies**, should list all of the relevant normal and abnormal studies required to construct a reasonable differential diagnosis: hemogram, blood chemistry, urine studies, arterial blood gases, microbiology results, tissue biopsy studies, miscellaneous studies (ECG, esophageal motility studies, etc), radiographic studies, polysomnographic studies. Authors should place normal values in parentheses when referring to unusual test results or values that have different normal ranges between laboratories. **What is the diagnosis?** Additional questions may also be included (ie, What study should be conducted next?) in addition to the diagnosis question. Alternative questions may focus on management alone when a manuscript does not present a diagnostic question (eg, end-of-life management issues). **Diagnosis:** State the diagnosis and the answers to any additional questions posed in the preceding "What is the diagnosis?". Do not provide explanatory text here but just mention the answers.

Discussion, using the present tense, present a clear discussion of the clinical condition that flows clearly from one topic to another. Most manuscripts should cover sequentially the topics of epidemiology, pathophysiology/etiology, clinical manifestations, approach to diagnosis, treatment and outcomes. Exceptions, such as manuscripts on end-of-life decision-making, should retain a clearly organized sequence of topics. Do not refer to the present patient in the body of the general discussion but instead refer back to the present patient in the Clinical Course section. Avoid in the Discussion stating the findings or opinions of others (eg, Jones and Smith reported…); instead, authors should synthesize the literature and state their views on the topic. **Clinical Course**, should take the general discussion back to the specific patient presented, informing readers how the diagnosis was established, how the care was managed and what outcomes occurred. **Pearls**, 3 to 5 important teaching points extracted from the Discussion. Pearls should represent concise, specific and clinically useful information rather than general statements of fact. **Suggested readings**, should be listed in chronological order with the oldest first and include a mix of classic and recent journal or book citations. References to general medical or nursing textbooks should be avoided.

Figures are needed only for the case presentation. In discussing figures in the case report, simply refer to their presence when the findings are sufficiently obvious to challenge the reader. If the finding is subtle and difficult to detect, the abnormality can be described in the case report, but in describing the figure do not provide the diagnosis or the answer to the question you will pose in the manuscript. When not mentioned in the case report, the abnormality in the figure should be discussed in the body of the discussion on the following page when referring in general to the condition and in the section on clinical course when providing follow-up for the patient presented. Authors may consider including an algorithm describing an approach to the clinical presentation.

Sample: Brownback KR, Crosser MS, Simpson SQ. A 49-year-old man with chest pain and fever after returning from France.Chest. 2012;141(6):1618-1621.Ultrasound Corner

Ultrasound Corner

1 **Article Element Requirements** Abstract length None Text length 1,600 words (of which case presentation should be up to 300 words, with the discussion being 900 words, including take-home points [ie, "Reverberations"]) Reference count 10; no references should appear before the Discussion Videos 2 or 3 video file sets (more than 1 video clip may be compiled for use in each video set),[a]: sets typically include 1) first step in diagnosis; 2) next step by ultrasonography or determination of diagnosis; 3) discussion video. Authors are responsible for creation and editing of videos, including addition of captioning and labeling.[b] Section editor will work with authors and CHEST to add voice-over narration of the discussion video on acceptance. Files names must be video1.XXX, video2.XXX, etc. and each Ultrasound Corner manuscript must have discussion video with the file name discussion.XXX (XXX is the file format). See past articles for the Discussion video format. Format 1) Introduction/ case presentation + initial examination video set (do not describe the ultrasonagram in a manner that would provide the answer to your question in #2; do mention the part of the body from which the ultrasonogram was obtained); 2) One question + one answer and follow-up ultrasonography video set; 3) Discussion + discussion video; 4) 3-4 "reverberations" (ie, take-home points); 5) references; 6) captions for figures if included; 7) short description of each video Other Written patient permission is required for publication; waivers may be considered on a case-by-case basis and must be approved by the Editor in Chief.

[a]*Video clips may be combined as needed.*

[b]*Authors should combine all needed video clips for each step into a single video file, using software such as Windows MovieMaker or Apple Final Cut Pro. For short ultrasound readings (eg, 2 or 3 seconds), authors should either loop the frames or copy the sequences several times so that viewers have a chance to absorb what they are seeing.* Correspondence

Correspondence

Letters

Letter to Editor, Response to Letter to Editor

1 **Article Element Requirements** Abstract length None Text length 400 words Reference count 5 references Other No No supplemental material. One figure or table permitted.

Letters to the Editor are intended for the clarification and edification of articles published in *CHEST*. It is up to the discretion of the Editor in Chief whether any Correspondence is sent for external peer review and whether to accept any letter for publication.

Commenting on Recent Articles

All letters commenting on previous articles should strive to provide constructive and respectful comments of the original work. Letters should pertain to articles published within the preceding 6 weeks. Any correspondence discussing recent *CHEST* articles should include a short original title that does not duplicate the title of the article. Authors should include the full citation of the complete article in the reference list. For letters responding to articles published to the Online First section, *CHEST* will hold publication until the final version of the article is published in a numbered issue of *CHEST*. All accepted letters will be sent to the corresponding author of the original article with an invitation to submit a response for publication.Response

Response Letters

Authors are asked to submit all replies to letters on their work within 2 weeks of receiving the invitation. If they do not respond within this time frame, the original letter will be published without a response. Authors should never correspond directly with the authors of correspondence. The replying author should also include the full reference to their original work and should submit the same conflict of interest information relevant to the original work. *CHEST* reserves the right to update the conflict of interest line in this regard as needed.Research Letters

Research Letters

1 **Article Element Requirements** Abstract length None Text length 1,000 words Reference count 10 references Other No No supplemental material; up to two figures and/or tables permitted.

Research Letters should be descriptions of focused research findings. The findings should be of high quality, be novel, or have potential clinical impact, but should not be advanced or large enough to warrant publication of a complete original research manuscript. Research Letters do not require an abstract. The text should include Introduction (not labeled), Methods, Results, and Discussion sections. They should follow the guidelines for Manuscript Preparation and Submission Requirements.General Interest

General Interest Commentary and Announcements

1 **Article Element Requirements** Abstract length None Text length 1,000 words Reference count 5 references Other No No supplemental material; one figure or table permitted.

CHEST will consider correspondence in the form of commentary of potential interest to readers, or that serves to announce matters of importance to the pulmonary, critical care, and sleep medicine community.

2. CONSORT Checklist:

Table 1 | CONSORT checklist of information to include when reporting randomised crossover trials

Section/topic	Item No	Description	Page No*
Title†	1a	Identification as a randomised crossover trial in the title	0
Abstract†	1b	Specify a crossover design and report all information outlined in table 2	1
Introduction:			
Background†	2a	Scientific background and explanation of rationale	2
Objectives‡	2b	Specific objectives or hypotheses	3
Methods:			
Trial design†	3a	Rationale for a crossover design. Description of the design features including allocation ratio, especially the number and duration of periods, duration of washout period, and consideration of carry over effect	3
Change from protocol‡	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants†	4a	Eligibility criteria for participants	3-4
Settings and location‡	4b	Settings and locations where the data were collected	3
Interventions†	5	The interventions with sufficient details to allow replication, including how and when they were actually administered	5-6
Outcomes‡	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	6
Changes to outcomes‡	6b	Any changes to trial outcomes after the trial commenced, with reasons	8
Sample size†	7a	How sample size was determined, accounting for within participant variability	6
Interim analyses and stopping guidelines‡	7b	When applicable, explanation of any interim analyses and stopping guidelines	6-7
Randomisation:			
Sequence generation‡	8a	Method used to generate the random allocation sequence	4
Sequence generation‡	8b	Type of randomisation; details of any restriction (such as blocking and block size)	4
Allocation concealment mechanism‡	9	Mechanism used to implement the random allocation sequence§ (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	4
Implementation†	10	Who generated the random allocation sequence,§ who enrolled participants, and who assigned participants to the sequence of interventions	4
Blinding‡	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	4-5
Similarity of interventions‡	11b	If relevant, description of the similarity of interventions	5-6
Statistical methods†	12a	Statistical methods used to compare groups for primary and secondary outcomes which are appropriate for crossover design (that is, based on within participant comparison)	6-7
Additional analyses‡	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7
Results			
Participant flow (a diagram is strongly recommended)†	13a	The numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome, separately for each sequence and period	8
Losses and exclusions†	13b	No of participants excluded at each stage, with reasons, separately for each sequence and period	8
Recruitment†	14a	Dates defining the periods of recruitment and follow-up	8
Trial end‡	14b	Why the trial ended or was stopped	8
Baseline data†	15	A table showing baseline demographic and clinical characteristics by sequence and period	4
Numbers analysed†	16	Number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	8
Outcomes and estimation†	17a	For each primary and secondary outcome, results including estimated effect size and its precision (such as 95% confidence interval) should be based on within participant comparisons.¶ In addition, results for each intervention in each period are recommended	9-10
Binary outcomes‡	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses‡	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing prespecified from exploratory	10-11
Harms†	19	Describe all important harms or untended effects in a way that accounts for the design (for specific guidance, see CONSORT for harms[32])	8
Discussion:			
Limitations†	20	Trial limitations, addressing sources of potential bias, imprecision, and if relevant, multiplicity of analyses. Consider potential carry over effects	14
Generalisability‡	21	Generalisability (external validity, applicability) of the trial findings	12-13
Interpretation†	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	12-14
Other information:			
Registration†	23	Registration number and name of trial registry	5
Protocol‡	24	Where the full trial protocol can be accessed, if available	
Funding‡	25	Sources of funding and other support (such as supply of drugs), role of funders	14

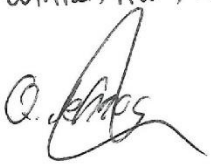
CONSORT=Consolidated Standards of Reporting Trials.
*Note: page numbers are optional depending on journal requirements.
†Modified original CONSORT item.
‡Unmodified CONSORT item.
§Random sequence here refers to a list of random orders, typically generated through a computer program. This should not be confused with the sequence of interventions in a randomised crossover trial, for example receiving intervention A before B for an individual trial participant.
¶A within participant comparison takes into account the correlation between measurements for each participant because they act as their own control, therefore measurements are not independent.

3. Eigenständigkeitserklärung:

Eigenständigkeitserklärung

Ich (de Groot, Quintin) erkläre hiermit, dass ich die vorliegende Arbeit selbständig, ohne Mithilfe Dritter und unter Benützung der angegebenen Quellen verfasst habe.

Ort, Datum: Winterthur, 17.05.2020

Unterschrift: 

4. Kritische Würdigung der eigenen Arbeit:

Studie: Comparison of two commercially available devices to measure nitric oxide lung diffusing capacity in healthy, non-smoking adults.

Eigene Leistung:

Meine eigene Leistung an dieser Forschungsarbeit hat schon im ersten Transferpraktikum begonnen. Ich stieg in ein schon geplantes Projekt zwischen den Standorten der Spitäler in Paris, Aachen und Zürich ein. Bei diesem Projekt, welches später als Pilotstudie eine Basis für diese Masterarbeit legte, wurde ein Vergleich zweier DLNO Messgeräte an den oben genannten Standorten durchgeführt. Meine Rolle bei diesem Projekt war die eines Probanden. Auf Basis der Erkenntnisse dieser Pilotstudie wurde binnen des Instituts für Epidemiologie, Biostatistik und Prävention die Forschungsfrage dieser Studie entwickelt. Da ich schon bei der zuvor durchgeführten Pilotstudie teilnahm und daher in diesem Fachgebiet eingelesen war, nahm ich dieses Projekt gerne als meine Masterarbeit an. Das Studiendesign stand zu Beginn fest, da es um einen Gerätevergleich handelt. Abgesehen vom Design war es mir jedoch möglich, Vorschläge für das detaillierte Vorgehen einzubringen und meine Meinung zu äußern. So hatte ich zu Beginn den Vorschlag, eine aktivitätsbezogene Intervention wie zum Beispiel 20 Kniebeugen miteinzubauen, um den Zusammenhang mit der Physiotherapie herzustellen. Nachdem vonseiten der ZHAW entschieden wurde, dass eine direkte physiotherapeutische Relevanz nicht mehr obligatorisch sei, konnte auf die endgültige Forschungsfrage fokussiert werden. Folglich konnte ich die Forschungsfrage ausarbeiten und einen detaillierten Ablauf in Zusammenarbeit mit meinem Betreuer planen. Mithilfe einer weiteren Kollegin war es möglich, die Messgeräte die Gegenstand der Studie waren, besser kennenzulernen und selbstorganisierte Probemessungen durchzuführen. Die Probandenrekrutierung außerhalb des Kollegen- und Bekanntenkreises des Institutes und des Universitätsspitals lag in meinem Aufgabenbereich. Auch die Durchführung eines großen Teils der Datenerhebung, sowie die Dateneingabe befanden sich in meiner Verantwortung. Nach Abschluss der Datenerhebung und der ersten Auswertungen wurde mit der Fehlersuche und der Problemlösung begonnen. Es mussten potenzielle

Quellen für die Entstehung des gemessenen Unterschiedes erörtert und der jeweilige mögliche Einfluss analysiert werden. Zusammenfassend kann gesagt werden, dass die Rahmenbedingungen sowie die Projektidee von meinem Betreuer gestellt wurden, ich jedoch binnen dieses Rahmens frei war, Ideen und Alternativen mit einzubringen und mitverantwortlich für die Durchführung, Analyse und Interpretation der Studie war.

Offene Fragen:

Die durchgeführte Studie zeigt auf, dass zwei Geräte binnen des Messverfahrens DLNO bei gleichen Individuen und Umgebungsfaktoren deutlich unterschiedliche Ergebnisse erzeugen. Nun stellt sich die Frage, ob zwei identische Geräte an verschiedenen Standorten vergleichbar messen. Falls dies der Fall sein sollte, könnte man Daten poolen, die auf einem identischen Gerät erhoben wurden. Da es momentan nur zwei auf dem Markt frei erhältliche Messgeräte gibt, könnte es trotz des Ergebnisses aus dieser Studie eine Möglichkeit geben, größere Datensätze als Referenzwerte zu generieren. Aufgrund verschiedener Geräte- und Softwareversionen der zwei Hersteller, wäre auch diesbezüglich ein Vergleich sinnvoll.

Kritische Betrachtung:

Offen bleibt zudem die Frage, ob innerhalb dieser Studie eine Einstellung an einem Gerät übersehen wurde, oder ob ein anderer unbekannter Fehler gemacht wurde. Trotz der Überprüfungen der Techniker und mehrfacher Kontrolle, sowie protokollierte Vorgehensweisen und Biomonitoring bleibt immer die Möglichkeit bestehen, dass eine mögliche Fehlerquelle nicht erkannt wurde. Diese Gefahr besteht jedoch in jeder durchgeführten Studie und nur eine Replikationsstudie könnte diese Art potenzieller Fehlerquellen aufdecken oder eliminieren.

Die Durchführung dieser Studie fand im Rahmen des Masterstudiums Physiotherapie der ZHAW statt. Daher war auch der zeitliche Ablauf sehr eng an die Rahmenbedingungen der ZHAW und der nebenbei anfallenden Studienlast gebunden. Prüfungsphasen, Semesterferien und Module, die auf spezifische Abschnitte der Masterarbeit zugeschnitten waren, bestimmten den zeitlichen Ablauf zu einem gewisses Maß. Hätte diese Bindung nicht existiert, wäre es möglich gewesen, diese

Forschungsarbeit in einem kürzeren zeitlichen Rahmen durchzuführen. Ein weiterer Grund, der für eine zwischenzeitliche Zwangspause gesorgt hatte, war eine leere Gasflasche und die entsprechende Lieferzeit der besagten Flasche. Nach einer fünfwöchigen Lieferzeit wurde diese kurz vor Weihnachten 2019 geliefert. Dies führte dazu, dass die Datenerhebung erst Mitte Januar anstelle von November/Dezember beendet werden konnte. Ab Februar entstanden erneut Schwierigkeiten bezüglich Besprechungsterminen und Terminen im Labor, aufgrund der Corona Pandemie.

Alternative Vorgehensweise:

In einer zukünftigen Replikationsstudie könnten verschiedene Maßnahmen getroffen werden, um einen Gerätevergleich zu optimieren. Zum einen wäre es wichtig, bei beiden Geräten die identische Gas-Mischung zu verwenden. Beide Geräte wurden jedoch in dieser Studie auf die jeweilige Gaskonzentration kalibriert, jedoch würde dies ein methodologisch optimierten Vergleich gewährleisten. Des Weiteren sollte eine externe Messmethode verwendet werden, um die Atem-Anhalte-Zeit (BHT) zu regulieren. Dies könnte beispielsweise mithilfe eines akustischen Signals gehandhabt werden. Ein solches Vorgehen würde den Einfluss des Programm-Interfaces minimieren. Die verwendeten Gasflaschen sollten regelmäßig kontrolliert werden und frühzeitig benötigte Gase bestellt werden. Eine weitere mögliche Verbesserung wäre, die Beschränkung der Verantwortlichkeit auf eine Person für die Durchführung der Messung zu kürzen. Dies würde einen potenziellen Einfluss von verschiedenen Messpersonen auf die Datenerhebung beseitigen. Im Rahmen dieser Masterstudie war dies aus Zeitgründen nicht möglich.

Relevanz der Masterarbeit:

Diese Studie hat nur bedingt eine Relevanz für die Physiotherapie. Innerhalb der Pneumologie und der Lungenfunktionsdiagnostik zeigt diese Studie jedoch eine sehr viel größere Relevanz. Wie in der Einleitung der Forschungsarbeit schon beschrieben, könnte dieses Verfahren helfen die Lungendiffusion und Krankheiten, bei denen dieser Prozess eingeschränkt ist, besser zu verstehen. Referenzwerte sind ein essenzieller Bestandteil, um individuelle Ergebnisse klinisch interpretieren zu können. In den

vergangenen Jahren wurden vermehrt Studien zur Generierung von Referenzwerten durchgeführt. Auch wurden diese Ergebnisse schon zusammengeführt, um die Aussagekraft zu vergrößern. Unsere Studie zeigt jedoch, dass dieser Schritt möglicherweise noch nicht gemacht hätte werden sollen. Wir haben aufgedeckt, dass man die Daten von den untersuchten Messgeräten nicht zusammenführen kann. Dies könnte später bei klinischer Anwendung im Ernstfall zu einer verfälschten medizinischen Diagnostik führen.

Die Relevanz für den Fachbereich der Physiotherapie besteht darin, dass dieses Verfahren gerade bei kardio-pulmonalen Patienten häufig einen elementaren Bestandteil darstellt. Daher hilft es zu gewährleisten, dass Patienten beispielsweise mit einer COPD, ein evidenzbasiertes diagnostisches Verfahren erhalten.

Generell ist nach momentanem Forschungsstand der Lungendiffusionsmessung mittels Stickstoffmonoxid noch nicht klar, welche Vorteile diese Messmethode mit sich bringt und ob diese jemals klinisch in Kombination zur DLCO Anwendung findet. Laut aktuellem Wissenstand könnte diese Methode, potenziell zu einem besseren Verständnis des Gasaustausches binnen der Lungenfunktionsdiagnostik führen. Diese Forschungsarbeit zeigt neue Erkenntnisse auf und beantwortet eine wichtige, bisher ungeklärte Forschungsfrage. Insgesamt hilft die durchgeführte Studie das Messverfahren mittels Stickstoffmonoxid besser zu verstehen und bringt damit den potenziellen Mehrwert einen Schritt näher an den Patienten.

Persönlicher Bezug:

Der Fachbereich Lungendiffusion war auch für mich als muskuloskelettaler Physiotherapeut etwas Unbekanntes. Nach langer Einarbeit binnen des ersten Transfermoduls und der beiden Messungen in Paris und Aachen, hat dieses Thema mein Interesse geweckt und ich habe es als sehr abwechslungsreich und erkenntniserweiternd empfunden, binnen der Pneumologie eine Forschungsarbeit durchgeführt zu haben. Meine bisherige Arbeitserfahrung hat sich sehr auf die physiotherapeutische Arbeit in Einzelpraxen konzentriert. Daher stellt diese Masterarbeit mit dem Einblick in den Fachbereich der inneren Medizin einen interdisziplinären, spannenden und herausfordernden Abschnitt des Masterstudiums dar.

5. Ethikkommission-Bewilligung:

Kanton Zürich
Kantonale Ethikkommission

Prof. Dr. med. Peter Meier-Abt
Präsident

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19th March 2019 / jam
BASEC -Nr. Req-2019-00226
Clarification of responsibility

Title: Comparison of two commercially available devices to measure nitric oxide lung diffusing capacity in healthy, non-smoking adults.

Dear Doctor Radtke

We refer to your submission dated 12/03/2019.

Your research project does not fall within the scope of the Human Research Act (HRA). Therefore, an authorization from the ethics committee is not required.

Kindly note that an invoice in the amount of CHF 200.- will be issued by the cantonal accounts department.

Sincerely yours,

Lea Schläpfer

6. Bestätigung der Betreuung:

Bestätigung der Betreuungsperson

Die betreuende Person, (Thomas Radtke) gibt ihr Einverständnis, dass die vorliegende Version als Masterarbeit eingereicht wird.

Ort, Datum: Zürich, 04.05.2020

Unterschrift: 

7. Curriculum Vitae des Verfassers:

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Education

2017 – present	**Master of Science in Physiotherapy** *ZHAW Zurich University of Applied Sciences (Switzerland)*
2013 – 2017	**Bachelor of Science in Physiotherapy** *Hogeschool Arnhem en Nijmegen (Netherlands)*
2012 – 2013	**Work & Travel** *New Zealand and Southeast-Asia*
2010 – 2012	**Specialized A-Levels (Social Services)** *Fachoberschule Kempten (Allgäu) (Germany)*
2005 – 2010	**Mittlere Reife** *Staatliche Realschule Kempten (Allgäu) (Germany)*

Work Experience

2020 – present	**Physiotherapist at Kantonspital Winterthur** Winterthur (Switzerland)
2017 – 2020	**Physiotherapist at Medbase Group** *Uzwil (Switzerland)*
Winter 2016/17	**Trainee Physiotherapist** *Wijkgezondheidscentrum Lindenholt (Nijmegen)*
Summer 2016	**Technical Representive BeNeLux** *Mammut Deutschland (BeNeLux)*
Winter 2015	**Trainee Physiotherapist** *Krankengymnastik Scholten Sulzberg (Germany)*

Courses

present	OMT- Osteopathic manual therapy
2016	Medical Taping
2014	Classical Taping
2013	Reanimation
2010	Extended First-Aid

Languages

Dutch:	Fluent
German:	Fluent
English:	Advanced
French:	Beginner